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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/848,780 | 05/03/2001 | Mitchell C. Sanders | 3265.1002-000 | 6635 |

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[REDACTED] EXAMINER

LIU, SAMUEL W

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1653 | 18 |

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|-----------------|----------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/848,780 | SANDERS, MITCHELL C. |
| Examiner | Art Unit | |
| Samuel W Liu | 1653 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 11 April 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 6-15 is/are pending in the application.

4a) Of the above claim(s) none is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 6-15 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>17</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The response filed 11 April 2003 (Paper No. 16) as to cancellation of claims 1-5 and addition of new claims 6-15, and applicant's petition for extension of time of two months have been entered. The following Office Action is applicable to the pending claims 6-15.

Please note that the rejection(s) not explicitly stated and/or restated below are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 6-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6, 8-9 and 11 recite "comprising an active domain in bacteria", the recitation is unclear as to what the "active domain" refers. The dependent claims are also rejected.

Claim 14 recites "an alpha-crystallin protein"; the recitation is indefinite as to whether or not the alpha-crystallin protein is the same protein recited in the first line of the claim, i.e., bovine alpha-crystallin protein. Also, claim 14 recites "the alpha crystallin protein in item c); the recitation is vague with regard to whether or not the claimed crystallin protein refers to the bovine alpha-crystallin protein or any alpha crystallin protein set forth in item c) of the claim. In addition, claim 14 is unclear regarding "size filtering" in item b) because it is unclear as to whether or not "size filtering" refers to filtering the sample through a filter paper (see page 10, lines 18-20), or purifying the claimed protein *via* gel filtration chromatography (see page 11,

lines 29-30). Further, claim 14 steps c) and d) appear to be the same step wherein buffering the alpha-crystallin protein to pH ~8 (step d) is a proviso for neutralizing the fraction comprising the crystallin protein (step c); thus, the order of the steps is ambiguous in this regard.

Claim 15 is indefinite in “coupled to a chromatography resin” because it is not clear as to whether or not “coupled to” refers to the bovine alpha-crystallin protein being covalently conjugated to a resin of the pre-column, or a chromatographic pre-column filter being “coupled to” a chromatographic resin during the purification process as claimed.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claims 6-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Ambrosius D. et al. et al. (US Pat. No. 6455279).

Ambrosius et al. teach a process of producing a naturally folded protein comprising expressing a target protein as a fusion protein with a molecular chaperone protein, wherein the chaperone protein is operatively linked with the target protein *via* a signal peptide that is fused to N-terminus of the protein (see the patent claims 1 and 7, column 2, lines 12-13, and column 4, lines 65-67), cleaving the chaperon protein-signal peptide portion from the target protein, and isolating the target protein thereof (see the patent claim 1). Additionally, Ambrosius et al. teach that the naturally-folded protein is water-soluble (see column 2, lines 46-52), and that the molecular chaperone is a small heat-shock protein (see column 2, lines 9-10), e.g., α A or α B-crystallin protein (see column 4, lines 3-5). The above Ambrosius' teachings meet the limitation set forth in claims 6-8 of instant application.

Ambrosius et al. teach that the patent invention is directed to a method of producing a water soluble protein (see column 2, lines 46-48) and that the molecular chaperone protein acts to increase soluble protein yield (see column 3, lines 53-56), which meets the limitation set forth in claim 9. Since Ambrosius et al. teach that α -crystallin type protein is employed as the molecular chaperon and that the signal peptide (locate at the up stream of the target protein) contains cleavage sequence, e.g., Ala-X-Ala (See column 4, lines 34-42), the above teachings are applied to claims 9-11 of the current application.

Also, Ambrosius et al. teach the molecular chaperone functions to stabilize proteins and thus protect them from aggregation and inactivation (see column 3, lines 30-32). Thus, the

above teaching as to the chaperone molecule-enhanced solubility of the target protein is also applicable to claims 12 and 13 of the instant application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 14 is rejected under 35 U.S.C. 103(a) as being obvious over Stevens A. *et al.* (*Curr. Eye Res.* (1987) 6, 739-740) taken with Reddy G. B. *et al.* (*J. Biol. Chem.* (2000) 275, 4565-4570).

Stevens et al. teach a method for purifying bovine alpha-crystallin protein using gel filtration chromatography comprising dissolving the alpha crystallin protein in a glycine solution (pH ~ 2.5). Stevens et al. do not expressly teach neutralizing the fraction containing the crystallin protein with a buffer to pH ~ 8.

It would have been obvious, however, for one of ordinary skill in the art to perform the gel filtration chromatography with the condition described by Stevens et al. followed by neutralizing the α -crystallin-containing fraction to pH approximately 8. This is because of the advantages of purification mean of Stevens, *i.e.*, (i) acidic condition in the presence of glycine allows for α -crystallin being well separated from β -crystallin chain, thereby avoiding β -crystallin chain contamination, and (ii) yield of such the purified α -crystallin is very high (greater than

95%). After the gel filtration chromatographic step, neutralizing acidic pH to pH ~ 8 as taught by Reddy et al. (see “Methods and Materials” section), therefore, would have been apparent to the skilled artisan to store the purified crystallin protein under near neural pH (e.g., approximately pH 8) for further use.

When combined the teachings of the above references, the skilled artisan would have expected success of performing the gel-filtration for purifying α -crystallin monomer and would have readily arrived at the invention set forth in claim 14. Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Conclusion

No claim is allowed.

Applicant’s amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

May 27, 2003

Christopher S. F. Low
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